

Systematic review and meta-analysis: Efficacy and safety of POEM for achalasia

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Abstract

Background: Peroral endoscopic esophageal myotomy (POEM) represents a less invasive alternative, as compared with conventional laparoscopic Heller myotomy for treating achalasia patients. In the last years, a number of prospective and retrospective experiences with POEM use for achalasia have been published.

Methods: Relevant publications in which patients affected by achalasia underwent POEM treatment were identified by *PubMed* databases for the period 2010 – 2013. From each study, we extracted the number and type of major complications (defined as those requiring any additional medical or surgical intervention). Data were pooled, using random-effects models. Heterogeneity among studies was assessed by using Cochran's *Q* and the I^2 statistic.

Results: We found 16 studies that provided data on 551 patients. The median surveillance period was 6 months (range: 3–12). The median of mean POEM duration was 156 minutes (range: 42–112). Median myotomy length was 10 cm (range: 6–14). Technical and clinical success were reported in 97% (95% CI: 94–98%) and 93% (407/428; 95% CI: 90–95%). No heterogeneity ($I^2 = 0\%$) or publication bias was present in both estimates. When limiting the analysis only to adverse events that require medical or surgical interventions, major adverse events occurred in 14% (95% CI: 11–17%); however, only one patient needed post-POEM surgery (0.2%; 95% CI: 0–0.5%).

Conclusions: POEM appeared to be a highly feasible and effective endoscopic treatment for achalasia. Despite POEM being apparently associated with relatively high morbidity, most patients are successfully managed conservatively, so that POEM appears as a very safe procedure; however, POEM should only be performed in centers able to treat POEM complications, such as pneumothorax or pneumoperitoneum.

Keywords

Achalasia, adverse events, complications, endoscopic esophageal myotomy, esophageal sphincter, esophagus, myotomy, peristalsis, review, safety, swallowing

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Introduction

Achalasia is a rare condition, of unknown causes, with an estimated annual incidence of one per 100,000 persons, characterised by a functional obstruction of the esophagus that is caused by failed relaxation of the lower esophageal sphincter (LES), in combination with absent peristalsis of the distal esophagus.¹

Patients mainly present with symptoms such as dysphagia for both solids and liquids, regurgitation of undigested food, respiratory complications, chest pain and weight loss. These symptoms result from impaired peristalsis and deficient or absent relaxation of the

LES, which leads to stasis of food in the esophagus.² Treatment aims to disrupt or dissect the LES, to enhance transport of the bolus into the stomach.

In the modern era of achalasia treatment, disruption of the LES is best accomplished by pneumatic dilation, using Rigiflex balloons or laparoscopic Heller myotomy (LHM), and less effectively, by

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pharmacological-type agents, such as *Clostridium botulinum* toxin injection or calcium channel blockers.^{3–7}

An innovative endoscopic method for dissection of the LES, using a needle-knife to cut the muscular fibers from the luminal side, was first described by Ortega et al.⁸ in 1980. Two decades later, Pasricha et al.⁹ first described the feasibility of an endoscopic submucosal esophageal myotomy in a survival animal model. Finally, Inoue et al.¹⁰ successfully performed the first peroral endoscopic esophageal myotomy (POEM) in humans, which appeared to be substantially less invasive, when compared with LHM. Following this preliminary experience, there have been published in the last years a number of prospective and retrospective experiences with POEM for achalasia, with controversial data in terms of adverse events and outcome.

The aim of this systematic review was to pool the results of POEM procedures, in terms of efficacy and safety, and also address relevant clinical and technical issues.

Methods

The methods of our analysis and inclusion criteria were based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.¹¹

Eligibility criteria

We considered all clinical studies for the period from 2010 (i.e. when POEM was first applied to human subjects) to December 2013, in which patients affected by achalasia underwent POEM treatment. Animal studies were excluded. If there was any suspicion of cohort overlap between studies, only the most recent study was considered for inclusion.

Information sources

A literature search was performed on December 2013. Relevant publications were identified by *PubMed*. Abstracts were not included, because they were unlikely to provide all the necessary details, in terms of adverse events. Additional references were located through searching the bibliographies of related papers. Our search was limited to papers written in English. Case series with less than or equal to three patients were also excluded. The medical terms ‘POEM’ and ‘achalasia’ were used in the search, with the following algorithm: ‘POEM[All Fields] OR “peroral endoscopic myotomy” [All Fields] AND (“esophageal achalasia” [MeSH Terms] OR (“esophageal” [All Fields] AND “achalasia” [All Fields]) OR “esophageal achalasia” [All Fields] OR “achalasia” [All Fields]’.

Study selection

Titles and abstracts of papers were screened by two reviewers. Any disagreements were resolved through discussion. Studies (the full report of the study) were independently pre-screened for relevance by two reviewers. Any disagreements were resolved through discussion. Data were extracted from relevant studies by one reviewer and checked by a second reviewer. Data from the included studies were extracted into tables. Any disagreements were resolved through discussion with a third reviewer. Information relating to the methodological quality of each study was also recorded.

Data collection process and list of items

From each report, reviewers independently abstracted:

- Year of publication;
- Country where the study was performed;
- Single- or multi-center study;
- Study design;
- Population characteristics;
- Number of patients included;
- Number of patients eligible;
- Mean age distribution;
- Sex distribution;
- Technical/clinical success;
- Rate of post-POEM esophagitis;
- Duration of follow up; and
- Rate of adverse events requiring medical/surgical treatment (self-limiting pneumo-mediastinum/-peritoneum not requiring any drainage/treatment was not considered as an adverse event).

Risk of bias in individual studies

Information was recorded relating to the methodological quality of each study. Quality assessment was performed using the STROBE checklist for observational studies.¹² More information can be found in Appendix 1.

Summary measures

The primary end-points of this systematic review were to address the following:

1. What are the feasibility and clinical success (defined as clinically-relevant improvement of dysphagia) rates of POEM?
2. What is the risk of clinically-relevant adverse events, after POEM?

Planned methods of analysis

Data on feasibility, efficacy and safety were extracted where possible. The prevalence of the main outcome variables in each study was combined, to yield a pooled prevalence with a 95% CI for all studies. Data were pooled using random-effects models, to generate a more conservative estimate of the prevalence. Heterogeneity among studies was assessed by using Cochran's Q (reported with a χ^2 -value and p -value) and the I^2 statistic, the latter describing the percentage of variation across studies that is due to heterogeneity, rather than chance, and presented with a 95% CI. Publication bias was measured using Egger's regression. Statistical analyses were carried out using the R statistical software package, version 2.15.2.¹³ $P < 0.05$ was considered statistically significant.

Results

Study selection

A flow diagram of this systematic review, with the number of papers retrieved, included and excluded, as well as the reasons for exclusion, is shown in Figure 1. In summary, 80 studies were identified by the included databases. After reviewing the title and abstract, 32 articles were retrieved as full text. Of these, 16 studies matched the inclusion criteria for our analysis.

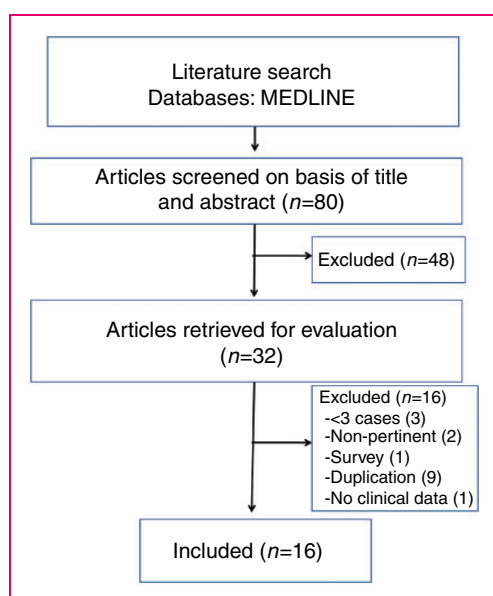


Figure 1. Flow chart of the systematic review.

MEDLINE: The US database of medical articles from journals, available online.

The reasons for exclusion of full-text studies are given in Appendix 2.

Characteristics of the included studies

Main characteristics of the included studies are provided in Table 1. Overall, three studies were performed in Europe, five in Asia and seven in the USA. A multi-centre international study was included in the analysis, too. Most of the studies were prospective, and in the few retrospective series a careful evaluation of the main variables was collected.

Participants

Overall, there were 551 subjects included in the selected series. Despite that there was some heterogeneity in the distribution of gender among the series, overall, 48% of the enrolled subjects were female. The median of the mean ages from all studies was 44 years (range: 32–64 years). Body mass index (BMI) was available only in four series (median 26; range: 25–27). All but three studies adopted a predefined score to assess the severity of dysphagia, being the Eckardt score in most of the cases.

Interventions

The characteristics of the interventions with POEM are reported in Table 2. Timing of POEM procedure was reported in all but two series. The median of the mean durations was 156 minutes (range: 42–112). Myotomy length was also available in all but three series. The median was 10 cm (range: 6–14).

Outcomes

Efficacy. Technical feasibility was reported in all the series. Across the studies, the prevalence of successfully-performed procedures varied from 71% to 100% (Figure 2). The pooled prevalence was 97% (95% CI: 94–98%). As is shown in Figure 2, no significant heterogeneity was detected in the analysis of technical feasibility ($\chi^2 = 13.59$, $p = 0.557$, $I^2 = 0\%$; 95% CI 0–47.3%). Publication bias was not statistically significant (Egger's regression: bias = −0.27; standard error (SE) = 0.6; $p = 0.697$).

The clinical success rate was reported by all but one series, which specifically looked only at adverse events. Across the studies, POEM was associated with a favorable clinical outcome in 466 out of 493 patients. The pooled rate of clinical success prevalence was 93% (95% CIs: 90–95%), with no statistically significant heterogeneity among studies ($\chi^2 = 13.86$, $p = 0.460$, $I^2 = 0\%$; 95% CI 0–53%), as is shown in Figure 3.

Table 1. Study and population characteristics of the included studies

Series	Country	Type	Patients (n)	Female, % (n)	Age, mean/median (range/SD)	BMI	Adopted score
Inoue ¹⁰	Japan	Prospective	17	7 (41)	41 (18–62)	NA	Dysphagia
Von Renteln ²⁰	Germany	Prospective	16	4 (25)	45 (26–76)	NA	Symptom score
Hungness ²¹	USA	Retrospective	18	5 (28)	38 (22–69)	25	Eckardt
Costamagna ²²	Italy	Retrospective	11	8 (73)	32 (24–58)	NA	Eckardt
Kurian ²³	USA	Prospective	40	23 (58)	53 (20–88)	26.8	NA
Veerlaan ²⁴	Netherlands	Prospective	10	4 (40)	43 (31–66)	NA	Eckardt
Chiu ²⁵	China	Prospective	16	5 (31)	48 (22–87)	NA	Dysphagia score
Minami ²⁶	Japan	Retrospective	28	19 (68)	52 (19–84)	NA	Eckardt
Meireles ²⁷	USA	Prospective	7	NA	42 (NA)	NA	NA
Rieder ²⁸	USA	Retrospective	4	3 (75)	64 ± 17	NA	NA
Lee ²⁹	Korea	Retrospective	13	10 (77)	40 ± 16	NA	Eckardt
Li ³⁰	China	Retrospective	238 (103 group A + 131 group B + 4 failed myotomy ^a)	122 (52)	37.6 ± 13.2; 41.5 ± 16.3	NA	Eckardt
Ujiki ³¹	USA	Retrospective	18	5 (28)	64.1 ± 4.8	25.3	Eckardt
Von Renteln ³²	International study	Prospective	70	30 (42.9)	45 (40–48)	NA	Eckardt
Khashab ³³	USA	Retrospective	9	5 (55)	38 (22–63)	NA	Eckardt
Teitelbaum ³⁴	USA	Prospective	36	11 (31)	45 ± 15	27	Eckardt

^aGroup A: full-thickness myotomy; Group B: circular muscle myotomy

BMI: body mass index; NA: no done

Publication bias was not statistically significant (Egger's regression: bias = 0.64; SE = 0.5; $p = 0.189$). The mean of the dysphagia scores was reduced from 7 to 1 ($p < 0.001$; Student test) in the series in which the Eckardt score was used (all but two). The median follow-up was 6 months (range: 3–12).

Safety. Post-POEM esophagitis was reported by most studies. The pooled rate was 13% (47 out of 354; 95% CI: 10–17%). When limiting the analysis to only adverse events that required medical/surgical intervention, the rate of adverse events was 14% (79 out of 551; 95% CI: 11–17%); however, only one patient needed post-POEM surgery (one out of 551 (0.2%); 95% CI: 0–0.5%). No POEM-related deaths occurred. The summarized results can be found in Table 3.

Risk of bias in individual studies

In most of the studies, it was unclear whether enrollment was actually consecutive, so that a selection bias cannot be completely excluded. The efficacy of POEM was mainly evaluated by a complex reference standard, such as post-POEM cardiac relaxation, the regression of dysphagia and the clinical scores. At least in theory,

the assessment of these variables should be independent from the POEM procedure, although all of the involved operators whom were not blinded to the procedure performed. See Appendix 1 and Appendix 3.

Discussion

According to our systematic review, POEM is a highly feasible, effective and safe procedure to treat achalasia. In a pooled population of 551 patients, we showed a technical feasibility of 97%. Moreover, in a subgroup of patients, we showed a 93% success rate, whilst the risk of adverse events requiring medical/surgical treatments was limited to 14% of the cases, resulting in surgery only in 0.2% of the initial population. Our results are relevant for the following reasons:

1. First, despite that any single study may appear underpowered to provide a reliable estimate of POEM efficacy, our pooled synthesis is associated with a limited 95% CI, showing a high degree of certainty on its precise estimate.
2. We did not detect any degree of heterogeneity in the efficacy estimate, showing the generalizability and reproducibility of the procedure. Of note, the

Table 2. Technical and clinical characteristics of POEM in the included series

	Timing, min (range/SD)	Myotomy length, cm (range)	Technical success, n (%)	Clinical success, n (%)	Pre-POEM Clinical Score	Post-POEM Clinical Score	Mean Follow up, in months (range)
Inoue ¹⁰	126 (100–180)	4.9 ^a /10.4 ^b (3–15)	17 (100)	16 (94)	10	1.3	5 (1–16)
Von Renteln ²⁰	114 (65–88)	12 (8–17)	16 (100)	15 (94)	8.8	1.4	3 (NA)
Hungness ²¹	113 (88–220)	9 (6–14)	18 (100)	16 (89)	7	1	6 (1–18)
Costamagna ²²	101 (75–140)	10.2–	10 (91)	10 (91)	7.1	1.1	3
Kurian ²³	131 (NA) ^c	9 (3–20)	40 (100)	39 (98)	NA	NA	6 (1–18)
Veerlaan ²⁴	NA	NA	10 (100)	10 (100)	8	1	3 (NA)
Chiu ²⁵	NA	10.8 (7–16)	16 (100)	16 (100)	2	0	NA (3.7–7.7)
Minami ³⁵	99.2 (61–160)	14.4 (10–18)	28 (100)	28 (100)	6.7	0.7	NA (3–28)
Meireles ²⁷	98	NA	5 (71)	5 (71)	NA	NA	NA (1–6)
Rieder ²⁸	NA (90–120)	6.5 (NA)	4 (100)	NA	NA	NA	NA
Lee ²⁹	NA	8.5 (NA)	13 (100)	13 (100)	6.4	0.4	6.9
Li ³⁰ ^ç	41.7 ± 18.9 48.9 ± 28.6	8 ± 1.3 in esophagus; 2.3 ± 0.5 in stomach	234 (98%)	210 (95) ^g	7.6 ± 2 group A; 8 ± 1.9 group B	1.2 ± 1.5 group A; 1.1 ± 1.3 group B	6.1 ± 4.3 group A 10.5 ± 3.8 group B
Ujiki ³¹	155.8 ± 12.8	11.2 ± 2.7	18 (100)	17 (94)	6.4 ± 0.5	0.7 ± 0.5	9.7 ± 2
Von Renteln ³²	105 (54–240)	13 (11.9–13.5)	68 (97)	42 (82) ^h	6.9	1	12
Khashab ³³	127 (90–164)	9.9 (NA)	9 (100)	9 (100)	NA	1	NA
Teitelbaum ³⁴	112 ± 36	NA	36 (100)	20/22 (91)	7 ± 2	1.5 (0–12)	12

^aEarlier phase.^bLater phase.^cSD ± 39.^dSD ± 34.^eSD ± 2.8.^fGroup A: full-thickness myotomy; Group B: circular muscle myotomy.^gComputed on 220 patients.^hComputed on 51 patients with 12 month follow up.

NA: Not applicable

included studies came from different continents, yet no particular difference between Asia and Western endoscopy appeared.

- Despite no direct comparison with LHM being available, the success rate we showed is so high that it is unlikely that any study will be able to detect a statistically significant difference between the two procedures. In particular, the long-term LHM success rate appeared to range between 73% and 92%.^{14–16}
- We showed that there was quite a high degree of homogeneity in the technical details, such as the length of myotomy and timing of the procedure, so that the technique appears to be already quite standardized.
- We showed that, on the one hand, POEM operators must be aware of adverse events that are not typical of non-POEM endoscopy, such as hypertensive pneumomediastinum and intra-mediastinum bleeding; but, on the other hand, such adverse events may be easily treated with decompressive actions, resulting at best in a short prolongation of hospital

stay; however, surgeons with extensive experience in esophageal surgery should always be promptly available to treat POEM adverse events.

- Despite that there are no comparative studies, POEM would appear as a more rational approach for achalasia, because it allows a more radical treatment of the hypertensive LES without the need of dilation repetition.
- In our systematic review, there was 13% of post-POEM esophagitis described. Such a rate would not appear higher than the 21% reported in a large randomized trial with LHM.³ This favorable rate, despite the lack of an anti-reflux plasty, could be related to the conservative nature of POEM, which does not imply the mobilization of the gastro-esophageal junction structures. Differently from LHM, POEM also allows for a more selective dissection of cardiac fibers.

There are limitations in our analyses. First, in most series, a selection bias could not be excluded, so that

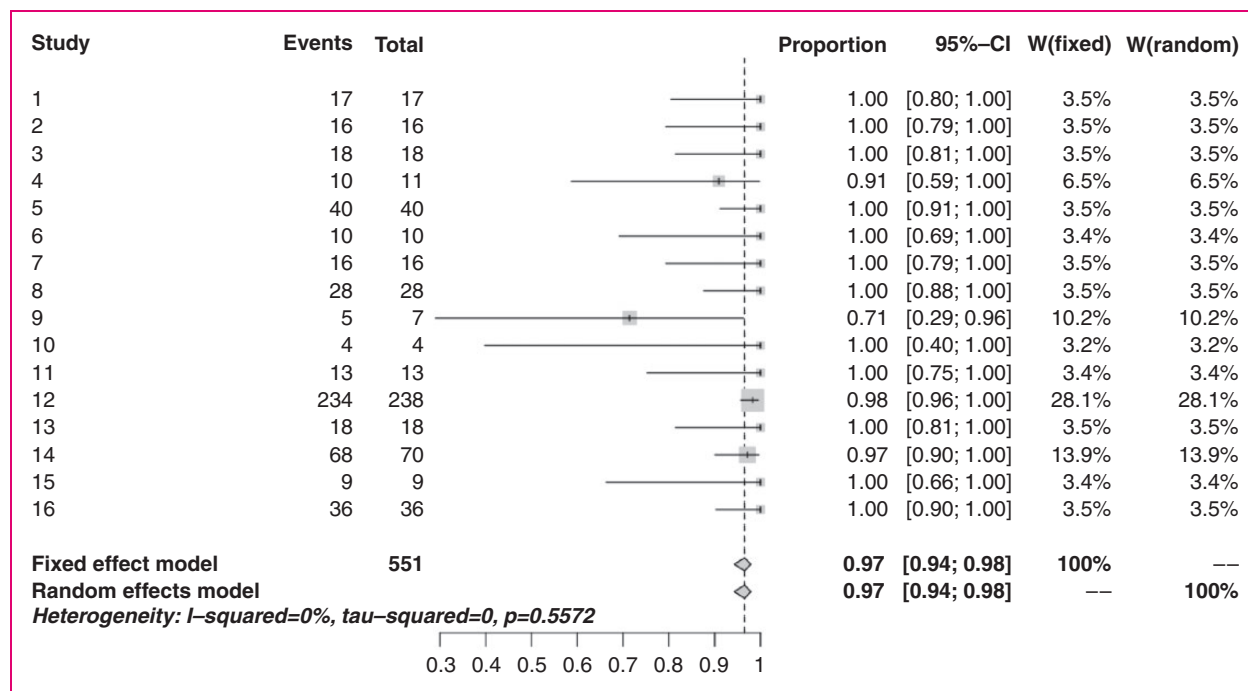


Figure 2. Forest plot of technical success rates and pooled estimates.

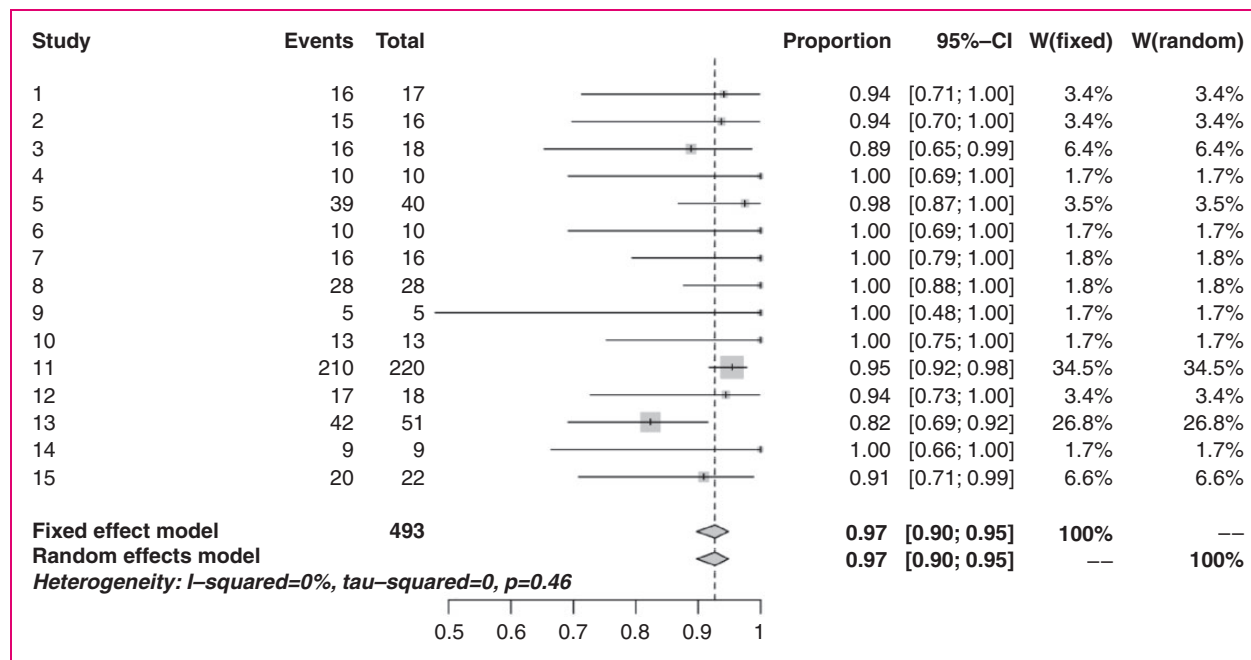


Figure 3. Forest plot: clinical success rates and pooled estimates.

POEM could be less successful when applied to unselected achalasia patients (i.e. those with a very dilated esophagus). Second, there were different criteria to measure the clinical degree of dysphagia or the adverse events rates. However, on the one hand, there was such

a dramatic improvement in any score that it is unlikely that the choice of such scores may have affected the results of our analysis; and on the other hand, the assessment of post-POEM surgery is a very solid surrogate for measuring POEM safety. Third, no

Table 3. Post-POEM complications in the collected studies

Paper and reference	Post-POEM esophagitis, n (%)	Major complication rate, n (%)	Post-POEM surgery, n (%)	Post-POEM death, n (%)
Inoue ¹⁰	1 ^a	0	0	0
Von Renteln ²⁰	1 (6)	9 ^b	0	0
Hungness ²¹	5 (28)	8 ^c	1	0
Costamagna ²²	0 (0)	2 ^e	0	0
Kurian ²³	NA	9 ^g	0	0
Veerlaan ²⁴	6 (60)	0	0	0
Chiu ²⁵	3 (19)	1 ^h	0	0
Minami ³⁵	11 (39.3)	3 ⁱ	0	0
Meireles ²⁷	NA	0	0	0
Rieder ²⁸	NA	0	0	0
Lee ²⁹	NA	0	0	0
Li ³⁰	20 (9)	26 ^m	0	0
Ujiki ³¹	NA	3 ⁿ	0	0
Von Renteln ³²	NA (grade A: 29.2%. Grade B: 12.3%) ^q	5 ^o	0	0
Khashab ³³	NA	0	0	0
Teitelbaum ³⁴	NA	13	0	0

^aPneumoperitoneum treated with puncture (n=1).

^bPneumoperitoneum treated with puncture (n=8). Also perforation treated with endoscopic clips (n=1) and cardiac ulcer treated conservatively (n=1).

^cPneumoperitoneum treated with needle decompression (n=7) and perforation treated with laparoscopy (n=1).

^eIntraoperative mucosal perforation treated with clips.

^gGastric/esophageal intraoperative perforation treated with clips (n=19), pneumoperitoneum treated with needle decompression (n=7), 1 pneumothorax treated with needle decompression (n=1), post-operative hematemesis (n=1), and leakage treated endoscopically with clips (n=1).

^hPneumonia treated with antibiotics and bronchial lavage.

ⁱBleeding (n=2), EJJ perforation between submucosal tunnel (n=1) and esophageal lumen treated with clip (n=1).

^mIntraoperative pneumoperitoneum treated with Verres needle decompression (n=2); intraoperative subcutaneous emphysema plus pneumothorax, treated with thoracic drainage (n=1); postoperative thoracic drainage (n=14); pleural effusion (n=2); fever $\geq 38^{\circ}$ (n=6); submucosal tunnel infection (n=1); epileptic seizure (n=1); and bleeding in submucosal tunnel (unspecified if treated or not) (n=1).

ⁿPneumoperitoneum treated with Verres decompression (n=3).

^oMucosal injury through electrocautery or laceration (n=3); bleeding requiring endoscopic hemostasis (n=1); and mediastinal hematoma requiring hospital readmission (n=1).

^qGroup A: full-thickness myotomy; Group B: circular muscle myotomy.

long-term follow-up results are yet available, because POEM is a recent novel technique. For instance, the short-term success of LHM was substantially higher than its long-term success rate.^{17–19} The same dynamic cannot yet be excluded for POEM.

In conclusion, we showed that POEM is a highly effective and safe procedure, when performed in a dedicated setting, and it also appeared to be reproducible and generalizable in different continents; however, when considering the observational type of studies included, we believe further data from randomized studies, as well as on the long-term outcome, are needed.

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Conflict of interest

The authors report there are no conflicts of interest.

References

1. Richter JE. Oesophageal motility disorders. *Lancet* 2001; 358: 823–828.
2. Cohen S. Motor disorders of the esophagus. *N Engl J Med* 1979; 301: 184–192.
3. Boeckstaens GE, Annese V, Des Varannes SB, et al. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia. *N Engl J Med* 2011; 364: 1807–1816.
4. Spechler SJ. Pneumatic dilation and laparoscopic Heller's myotomy equally effective for achalasia. *N Engl J Med* 2011; 364: 1868–1870.
5. Yaghoobi M, Mayrand S, Martel M, et al. Laparoscopic Heller's myotomy versus pneumatic dilation in the treatment of idiopathic achalasia: A meta-analysis of randomized, controlled trials. *Gastrointest Endosc* 2013; 78: 468–475.
6. D'Onofrio V, Annese V, Miletto P, et al. Long-term follow-up of achalasic patients treated with botulinum toxin. *Dis Esophag* 2000; 13: 96–103.
7. Annese V, Bassotti G, Coccia G, et al. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. *Gut* 2000; 46: 597–600.
8. Ortega JA, Madureri V and Perez L. Endoscopic myotomy in the treatment of achalasia. *Gastrointest Endosc* 1980; 26: 8–10.
9. Pasricha PJ, Hawari R, Ahmed I, et al. Submucosal endoscopic esophageal myotomy: A novel experimental approach for the treatment of achalasia. *Endoscopy* 2007; 39: 761–764.
10. Inoue H, Minami H, Kobayashi Y, et al. Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy* 2010; 42: 265–271.
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. *Ann Intern Med* 2009; 151: W65–W94.
12. Von Elm E, Altman DG, Egger M, et al. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *Brit Med J* 2007; 335: 806–808.

13. R Foundation for Statistical Computing V. R: A language and environment for statistical computing, wwwR-project.org (2008, accessed day Month year).
14. Csendes A, Braghetto I, Burdiles P, et al. Very late results of esophagomyotomy for patients with achalasia: Clinical, endoscopic, histologic, manometric and acid reflux studies in 67 patients for a mean follow-up of 190 months. *Ann Surg* 2006; 243: 196–203.
15. Zaninotto G, Rizzetto C, Zambon P, et al. Long-term outcome and risk of oesophageal cancer after surgery for achalasia. *Br J Surg* 2008; 95: 1488–1494.
16. Cowgill SM, Villadolid D, Boyle R, et al. Laparoscopic Heller myotomy for achalasia: Results after 10 years. *Surg Endosc* 2009; 23: 2644–2649.
17. Hunter JG, Trus TL, Branum GD, et al. Laparoscopic Heller myotomy and fundoplication for achalasia. *Ann Surg* 1997; 225: 655–665.
18. Rosati R, Fumagalli U, Bona S, et al. Evaluating results of laparoscopic surgery for esophageal achalasia. *Surg Endosc* 1998; 12: 270–273.
19. Rebecchi F, Giaccone C, Farinella E, et al. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia: Long-term results. *Ann Surg* 2008; 248: 1023–1030.
20. Von Renteln D, Inoue H, Minami H, et al. Peroral endoscopic myotomy for the treatment of achalasia: A prospective single center study. *Am J Gastroenterol* 2012; 107: 411–417.
21. Hungness ES, Teitelbaum EN, Santos BF, et al. Comparison of perioperative outcomes between peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy. *J Gastrointest Surg* 2013; 17: 228–235.
22. Costamagna G, Marchese M, Familiari P, et al. Peroral endoscopic myotomy (POEM) for oesophageal achalasia: Preliminary results in humans. *Dig Liver Dis* 2012; 44: 827–832.
23. Kurian AA, Dunst CM, Sharata A, et al. Peroral endoscopic esophageal myotomy: Defining the learning curve. *Gastrointest Endosc* 2013; 77: 719–725.
24. Verlaan T, Rohof WO, Bredenoord AJ, et al. Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointest Endosc* 2013; 78(1): 39–44.
25. Chiu PW, Wu JC, Teoh AY, et al. Peroral endoscopic myotomy for treatment of achalasia: From bench to bedside. *Gastrointest Endosc* 2013; 77: 29–38.
26. Minami H, Isomoto H, Yamaguchi N, et al. Peroral endoscopic myotomy for esophageal achalasia: Clinical impact of 28 cases. *Dig Endosc* 2014; 26: 43–51.
27. Meireles OR, Horgan S, Jacobsen GR, et al. Transesophageal endoscopic myotomy (TEEM) for the treatment of achalasia: The US human experience. *Surg Endosc* 2013; 27: 1803–1809.
28. Rieder E, Swanstrom LL, Perretta S, et al. Intraoperative assessment of esophagogastric junction distensibility during peroral endoscopic myotomy (POEM) for esophageal motility disorders. *Surg Endosc* 2013; 27: 400–405.
29. Lee BH, Shim KY, Hong SJ, et al. Peroral endoscopic myotomy for treatment of achalasia: Initial results of a Korean study. *Clin Endosc* 2013; 46: 161–167.
30. Li QL, Chen WF, Zhou PH, et al. Peroral endoscopic myotomy for the treatment of achalasia: A clinical comparative study of endoscopic full-thickness and circular muscle myotomy. *J Am Coll Surg* 2013; 217: 442–451.
31. Ujiki MB, Yetasook AK, Zapf M, et al. Peroral endoscopic myotomy: A short-term comparison with the standard laparoscopic approach. *Surgery* 2013; 154: 893–900.
32. Von Renteln D, Fuchs KH, Fockens P, et al. Peroral endoscopic myotomy for the treatment of achalasia: An international prospective multicenter study. *Gastroenterology* 2013; 145: 309–311.
33. Khashab MA, Messallam AA, Saxena P, et al. Jet injection of dyed saline facilitates efficient peroral endoscopic myotomy. *Endoscopy* 2014; 46: 298–301.
34. Teitelbaum EN, Soper NJ, Arafat FO, et al. Analysis of a learning curve and predictors of intraoperative difficulty for peroral esophageal myotomy (POEM). *J Gastrointest Surg* 2014; 18: 92–99.
35. Minami H, Yamaguchi N, Matsushima K, et al. Improvement of endocytoscopic findings after peroral endoscopic myotomy (POEM) in esophageal achalasia: Does POEM reduce the risk of developing esophageal carcinoma? Per oral endoscopic myotomy, endocytoscopy and carcinogenesis. *BMC Gastroenterol* 2013; 13: 22.
36. Familiari P, Marchese M, Gigante G, et al. Peroral endoscopic myotomy for the treatment of achalasia in children. *J Pediatr Gastroenterol Nutr* 2013; 57: 794–797.
37. Kurian AA, Bhayani NH, Reavis K, et al. Endoscopic suture repair of full-thickness esophagotomy during peroral esophageal myotomy for achalasia. *Surg Endosc* 2013; 27: 3910.
38. Muller M, Eckardt AJ and Wehrmann T. Endoscopic approach to achalasia. *World J Gastrointest Endosc* 2013; 5: 379–390.
39. Saxena P, Chavez YH, Kord Valeshabad A, et al. An alternative method for mucosal flap closure during peroral endoscopic myotomy using an over-the-scope clipping device. *Endoscopy* 2013; 45: 579–581.
40. Stavropoulos SN, Modayil RJ, Friedel D, et al. The International Per Oral Endoscopic Myotomy Survey (IPOEMS): A snapshot of the global POEM experience. *Surg Endosc* 2013; 27: 3322–3338.
41. Teitelbaum EN, Rajeswaran S, Zhang R, et al. Peroral esophageal myotomy (POEM) and laparoscopic Heller myotomy produce a similar short-term anatomic and functional effect. *Surgery* 2013; 154: 885–892.
42. Teitelbaum EN, Boris L, Arafat FO, et al. Comparison of esophagogastric junction distensibility changes during POEM and Heller myotomy using intraoperative FLIP. *Surg Endosc* 2013; 27: 4547–4555.
43. Zhou PH, Li QL, Yao LQ, et al. Peroral endoscopic remyotomy for failed Heller myotomy: A prospective single-center study. *Endoscopy* 2013; 45: 161–166.
44. Cai MY, Zhou PH, Yao LQ, et al. Peroral endoscopic myotomy for idiopathic achalasia: Randomized comparison of water-jet assisted versus conventional dissection technique. *Surg Endosc* 2014; 28(4): 1158–1165.

45. Ren Z, Zhong Y, Zhou P, et al. Perioperative management and treatment for complications during and after peroral endoscopic myotomy (POEM) for esophageal achalasia (EA). *Surg Endosc* 2012; 26: 3267–3272.
46. Bhayani NH, Kurian AA, Dunst CM, et al. A comparative study on comprehensive, objective outcomes of laparoscopic Heller myotomy with peroral endoscopic myotomy (POEM) for achalasia. *Ann Surg* 2014; 259: 1098–1103.
47. Swanstrom LL, Kurian A, Dunst CM, et al. Long-term outcomes of an endoscopic myotomy for achalasia: The POEM procedure. *Ann Surg* 2012; 256: 659–667.
48. Swanstrom LL, Rieder E and Dunst CM. A stepwise approach and early clinical experience in peroral endoscopic myotomy for the treatment of achalasia and esophageal motility disorders. *J Am Coll Surg* 2011; 213: 751–756.
49. Sharata A, Kurian AA, Dunst CM, et al. Peroral endoscopic myotomy (POEM) is safe and effective in the setting of prior endoscopic intervention. *J Gastrointest Surg* 2013; 17: 1188–1192.
50. Onimaru M, Inoue H, Ikeda H, et al. Peroral endoscopic myotomy is a viable option for failed surgical esophagomyotomy instead of redo surgical Heller myotomy: A single center prospective study. *J Am Coll Surg* 2013; 217: 598–605.

Appendix 1. Assessment of risk of individual bias

Potential bias <i>et al.</i>	13	22	23	240	25	262	27	28	29	30	31	32	33	34	35	37
1. Was the spectrum of patients representative of the patients who will receive the test in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Were selection criteria clearly described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
3. Is the reference standard likely to correctly classify the target condition?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
5. Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Did patients receive the same reference standard regardless of the index test result?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Was the reference standard independent of the index test i.e. the index test did not form part of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8. Was the execution of the index test described in sufficient detail to permit replication of the test?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
9. Was the execution of the reference standard described in sufficient detail to permit its replication?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Were the index test results interpreted without knowledge of the results of the reference standard?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Were the reference standard results interpreted without knowledge of the results of the index test?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
12. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
13. Were withdrawals from the study explained?	Y	Y	N	N	Y	Y	Y	N	Y	N	N	N	N	Y	N	Y

Appendix 2. Articles excluded and main reasons

Familiari ³⁶	≤3 cases
Kurian ³⁷	≤3 cases
Muller ³⁸	Non-pertinent
Saxena ³⁹	≤3 cases
Stavropoulos ⁴⁰	Survey
Tietelbaum ⁴¹	Partial duplication
Tietelbaum ⁴²	No clinical outcome
Zhou ⁴³	Partial duplication
Cai ⁴⁴	Partial duplication
Ren ⁴⁵	Partial duplication
Minami ³⁵	Partial duplication
Bhayani ⁴⁶	Partial duplication
Swanstrom ⁴⁷	Partial duplication
Swanstrom ⁴⁸	Partial duplication
Sharata ⁴⁹	Partial duplication
Onimaru ⁵⁰	Population non representative